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Impact of Lifestyle Modification on Diabetic Kidney Disease

Chijoke Onyenwenyi, MD and

Department of Medicine, Division of Nephrology, The University of Illinois at Chicago, 820 South Wood Street, 418W CSN, MC 793, Chicago, IL 60612, Phone (312) 996-6736, Fax (312) 996-7378, conyenwe@uic.edu

Ana C. Ricardo, MD, MPH

Department of Medicine, Division of Nephrology, The University of Illinois at Chicago, 820 South Wood Street, 418W CSN, MC 793, Chicago, IL 60612, Phone (312) 996-8392, Fax (312) 996-7378, aricar2@uic.edu

Abstract

Kidney disease is common in patients with type 1 and type 2 diabetes mellitus and is associated with adverse health outcomes, including progression to end-stage renal disease. In the general population, adherence to a healthy lifestyle is known to reduce the risk of cardiovascular events and death. Among individuals with diabetic kidney disease, modifications in lifestyle factors, including diet, physical activity, smoking habits and body mass index, represent a promising cost-effective therapeutic adjunct to pharmacologic treatment of kidney disease incidence and progression.

Keywords

Diabetic kidney disease; lifestyle; diet; physical activity; smoking; obesity

Introduction

Diabetic kidney disease is a major public health problem that affects approximately one third of individuals with type 1 and type 2 diabetes mellitus worldwide. [1–4] Patients with diabetic nephropathy are at heightened risk of progression to end-stage renal disease (ESRD), cardiovascular disease and death. [5–7] Therefore, the importance of identifying effective interventions to prevent or halt the progression of diabetic kidney disease cannot be overemphasized. In the general population, as well as in individuals with chronic kidney disease (CKD), adherence to a healthy lifestyle that involves regular physical activity, a healthy diet (e.g. rich in fruits, vegetables, whole grains, and low in fat), and abstinence from smoking, has been shown to improve survival from cardiovascular events and death.

Correspondence to: Ana C. Ricardo.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Chijoke Onyenwenyi declares no conflict of interest.

[8–12] In this report, we will review the evidence accumulated from epidemiologic and clinical research studies regarding the impact of four lifestyle-related factors (diet, physical activity, smoking habits, and obesity) on diabetic kidney disease incidence and progression (Table 1).

Diet and Diabetic Kidney Disease

Given the high prevalence of multiple metabolic derangements in patients with diabetic kidney disease, delivery of individualized dietary counseling based on culture, disease severity, blood pressure, phosphorus and potassium levels may be ideal. Preferably, tailored dietary interventions should occur in the context of an educational program. [13] A review of each one of the dietary factors which could impact diabetic kidney disease [13–15] is beyond the scope of this review. We decided to focus on the effect of low protein diet on diabetic kidney disease given the amount and quality of research studies conducted to evaluate this association. However, it is important to note that dietary sodium restriction appears to offer the greatest benefit in patients with proteinuria and CKD progression, including those with diabetes. [16–18]

Increased protein intake has been shown to be deleterious to the kidneys in animal models of diabetic nephropathy [19]. It has long been thought that a high protein intake led to increased renal blood flow, glomerular filtration and glomerular hypertension [20]. Protein intake is also thought to modulate the intrarenal renin angiotensin aldosterone system (RAAS), [21,22] and low protein diet may exert renoprotective effects similar to RAAS blockade with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) (Figure 1). These observations have led to several studies examining the effect of low protein diet on diabetic kidney disease with varying results.

To determine if dietary protein restriction (0.8 g/kg/day) delayed the onset of diabetic nephropathy, Pijls *et al* [23] conducted a randomized trial of 121 patients with type 2 diabetes. At 6 and 12 months, the 24-hr urine albumin excretion was significantly lower in the experimental group compared to the usual protein intake group, even after adjustment for blood pressure. However, this findings were not replicated in later study by the same authors. [24] Another study examining the effect of low (0.8 g/kg/day) vs. usual protein diet on estimated glomerular filtration rate (eGFR) and urine albumin excretion rate (AER) in 60 patients with type 2 diabetes, [25] found no significant changes in outcomes among participants with normo- or microalbuminuria at baseline. However, in participants with macroalbuminuria, a low protein diet was associated with an increase in creatinine clearance from baseline to the end of follow-up (17.9 ml/min) compared with a decline in the control group (–9.3 ml/min; $p<0.05$). In addition, AER was significantly reduced in the low protein group (1281 to 444 mg/24hr; $p<0.05$). In contrast, in another randomized controlled study of 112 patients with type 2 diabetes and established nephropathy [26], a low protein diet (0.8 g/kg/day) did not appear to modify eGFR compared with a normal protein diet (1.2 g/kg/day) during the 5 years of follow-up. Similar negative findings have been reported by others. [27]

Studies in patients with type 1 diabetes have also shown heterogeneous results. Hansen *et al* [28], in a 4-year randomized trial comparing low protein diet (0.6 g/kg/day) with usual protein diet in 82 individuals with type 1 diabetes and nephropathy, reported a significant reduction in the risk ESRD or death (relative risk 0.23, $p=0.01$), even after adjustment for cardiovascular disease at baseline. An earlier study by Raal *et al* [29] randomly assigned 22 subjects with type 1 diabetes to a protein restricted diet (0.8 g/kg/day) or a unrestricted protein diet (1.6 g/kg/day). They found that GFR declined in the unrestricted protein diet group (66 to 58 ml/min/1.73m²; $p=0.01$) but did not change in the low protein diet group (50 to 53 ml/min/1.73m²). There was no change in the degree of proteinuria in the unrestricted protein group while the low protein diet group showed a significant decrease in proteinuria (2.15 to 1.13 g/24hr; $p=0.002$).

Several meta-analyses of randomized trials on the effects of protein restriction on diabetic kidney disease have been performed, not surprisingly also with varying results. Nezu *et al*, [30] analyzed data from 13 randomized trials comparing low protein diet versus control with a total of 779 participants with type 1 and 2 diabetes. The authors concluded that a low protein diet was associated with a significant improvement in GFR (5.82 ml/min/1.73m², 95% CI 2.30–9.33), and this effect was consistent across subgroups of types of diabetes and stages of diabetic kidney disease. However, proteinuria did not differ between the intervention and control groups. It is important to mention that since poor compliance with low protein diet was noted in several of these randomized trials, the authors conducted a sensitivity analysis to account for diet compliance and found that the effect of low protein diet on GFR occurred only in patients with fair compliance. Another meta-analysis [31] of 8 randomized trials with a total of 519 participants with type 1 and 2 diabetes found no significant association of low protein diet with improvement in GFR. However, they found a significant benefit of low protein diet on proteinuria though the authors recommended that this finding be interpreted with caution given that different methods were used to measure proteinuria.

Why are there conflicting data regarding the effect of a low protein diet on diabetic kidney disease? First, it must be noted that studies involving dietary interventions are difficult to conduct for multiple reasons, including participants' compliance. In some studies, the differences in protein intake between the low protein diet and control group were minimal, and decreased over time [23,24]. Other studies failed to achieve the prescribed amount of protein intake. [26–28] Secondly, some of the studies had short intervention periods, which may not have been enough to detect an effect. Third, the typical diet in most Western countries has high sodium content, which could be a potential confounder of the association between protein diet and diabetic kidney disease. High sodium intake can blunt the antihypertensive and antiproteinuric effects of ACEI and ARB due to activation of the renal renin-angiotensin system. In a similar fashion, a diet with high sodium content could mask the renoprotective effects of low dietary protein which is thought to work by decreasing plasma renin activity. [32]

It is still unclear whether dietary protein restriction slows the progression of diabetic kidney disease. Recognizing the potential benefits and known risks associated with various levels of dietary protein, the Kidney Disease Improving Global Outcomes (KDIGO) and the National

Kidney Foundation (NKF) suggest a target dietary protein intake of 0.8 g/kg/day for people with or without diabetes and eGFR <30 ml/min/1.73m² accompanied with nutrition education and close monitoring of clinical and biochemical parameters. [13,33] For instance, the recommended intake of protein for a 70 kg person would be 56 g of protein per day which would correspond to eating 3 servings of ~18.5 g of protein each. Examples of a 18.5 g of protein serving include 74 g (~2.4 oz) of canned tuna or turkey breast, and 180 g (~6.5 oz) of fat-free Greek yogurt.

Physical Activity and Diabetic Kidney Disease

Physical activity has been associated with improved physical fitness, blood pressure, lipid profile, [34,35] insulin sensitivity, [36] and cardiovascular outcomes [37] in persons with diabetes. While acute exercise has been shown to cause a transient increase in proteinuria, in the long term regular exercise has been shown to improve proteinuria in rat models of diabetes. [38] However, few clinical studies have examined the effects of physical activity on diabetic kidney disease.

Cross-sectional and longitudinal studies have shown high prevalence of diabetic kidney disease in individuals with low levels of physical activity. [39–42] In the Finnish Diabetic Nephropathy (FinnDiane) Study, which is a prospective cohort study of over 1400 individuals examining clinical, environmental, metabolic and genetic risk factors for complications of type 1 diabetes, Waden *et al.* [39] reported that leisure time physical activity (LTPA) intensity (defined as a subjective degree of self-reported shortness of breath and sweating) was associated with progression from normo- to microalbuminuria. During 8 years of follow-up, the cumulative progression rate was 15.4%, 6.9%, and 5.9% in the low, moderate, and high intensity groups, respectively (p=0.047). However, after multivariable adjustment these differences became less significant. Furthermore, frequency and duration of physical activity were not associated with progression from normo- to microalbuminuria. Similarly, another large observational study of patients with type 2 diabetes [41] showed that compared with sedentary participants, individuals who self-reported daily physical activity had a significantly reduced risk of CKD incidence or progression (defined as GFR decline > 5% per year, progression to ESRD, microalbuminuria, or macroalbuminuria at 5.5 years). This was in contrast to the findings from a retrospective analysis of data from the Diabetes Control and Complications Trial (DCCT) [43] which found no association between the self-reported weekly intensity of physical activity and the development of urine AER >40 mg/24 hour over a mean follow-up of 6.5 years.

It is important to note that most of the studies cited relied on subjective, self-reported measures of physical activity which could be subject to recall bias. However, in view of the known overall health benefits of physical activity, the American Diabetes Association recommends at least 150 min per week of moderate to vigorous aerobic exercise at least 3 days a week for patient with type 2 diabetes. Individuals with type 1 diabetes can also take part in physical activity if they do not have severe complications. [44] Health care providers should be aware of potential barriers to physical activity in patients with diabetes which include the fear of hypoglycemia (which can be prevented by adjustment of pre-exercise insulin and carbohydrate intake) and low fitness levels. [45], [46]

Smoking and Diabetic Kidney Disease

Smoking is thought to induce renal damage by several mechanisms including increased oxidative stress, [47] activation of growth factors [48–50], and endothelial dysfunction [51,52]. Structural lesions of the kidney related to smoking include myointimal hyperplasia [53] and idiopathic nodular glomerulosclerosis. [54] The association between cigarette smoking and diabetic nephropathy was first reported in 1978 by Christiansen. [55] Since then, numerous cross-sectional and longitudinal studies have provided evidence of the deleterious effects of smoking on kidney function, including prevalent and incident albuminuria, progression from micro- to macroalbuminuria, as well as GFR decline. A large cross-sectional study from the Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND) [56] which evaluated more than 24,000 individuals with type 2 diabetes from 33 countries, found that smoking was independently associated with prevalent micro- or macroalbuminuria (OR 1.15, $P<0.01$). Another study of 359 men and women with type 1 diabetes, [57] reported that the prevalence of increased AER ($>7.6 \mu\text{g}/\text{min}$) was 2.8 times higher in smokers compared with non-smokers. Smoking remained a significant risk factor for albuminuria even after adjusting for age, blood pressure and HbA_{1c} levels. More importantly, albuminuria improved significantly after smoking cessation. Similarly, an analysis of data from the European Diabetes Insulin Dependent Diabetes Mellitus (EURODIAB IDDM) Complications Study [58] showed that current smokers had higher risk of albuminuria (AER >20) compared with participants who never smoked (OR 1.6 for men, and 1.5 for women, $p<0.05$) after adjustment for age, duration of diabetes, education, systolic blood pressure and HbA_{1c}.

Cigarette smoking has also been associated with incident microalbuminuria. A prospective study of 137 individuals with type 1 diabetes and normoalbuminuria [59] showed that a significantly higher proportion of smokers progressed to persistent microalbuminuria compared with non-smokers (14% vs. 3%, $p=0.03$) during 4 years of follow-up. In another prospective cohort of 537 individuals with type 1 diabetes and normoalbuminuria, smoking was found to be a significant predictor of incident micro- and macroalbuminuria (relative risk 1.61, $P<0.02$). [60] In addition, cigarette smoking has been associated with progression of diabetic kidney disease in both type 1 and type 2 diabetes. In a prospective study of 96 patients with type 1 diabetes and diabetic nephropathy (defined as persistent proteinuria and the presence of diabetic retinopathy), Sawicki *et al.* [61] reported that progression of nephropathy over the course of one year was more common in smokers compared with non-smokers (53% vs. 11%). Likewise, in a prospective study of 182 patients with type 2 diabetes living in Japan, smokers had an increased risk of ESRD (hazard ratio 1.53, $p=0.04$) compared with non-smokers after adjustment for urinary protein excretion; however, this association was attenuated after adjusting for other covariates. [62]

Fewer studies have evaluated the association between smoking and glomerular filtration rate. The largest study was reported by de Boer *et al.* [63] in an observational extension of the DCCT including over 1000 individuals with type 1 diabetes and normoalbuminuria. During 5.8 years of follow-up, a greater rate of decline in creatinine clearance was observed in active versus nonactive smokers (-0.77 versus $-0.18 \text{ ml}/\text{min}/1.73 \text{ m}^2/\text{year}$). Of note, no

significant association between active smoking and incident microalbuminuria was found. In a smaller study of 227 patients with type 2 diabetes and nephropathy followed for 6.5 years, a more rapid GFR decline (measured by ^{51}Cr -EDTA) was independently associated with heavy smoking (>20 cigarettes/day). [64] In contrast, Hovind *et al* [65] in a prospective study of 300 individuals with diabetic kidney disease (defined as persistent albuminuria $>300\text{mg}/24\text{h}$) found that smoking was not associated with a decline in GFR during 3 years of follow-up. The reason for these discrepant findings is unclear but has been attributed to differences in study design, methods of measuring GFR and length of follow-up.

In summary, several cohort studies have demonstrated the adverse impact of smoking on renal function. These findings, added to the evidence of the negative effects of smoking on cardiovascular and overall health, provide sufficient evidence to encourage avoidance and quitting of smoking in patients with established or at risk of diabetic kidney disease as recommended by KDIGO. [13]

Obesity and Diabetic Kidney Disease

Obesity is associated with multiple health risks including hypertension [66,67], cardiovascular disease [68], obstructive sleep apnea [69], and osteoarthritis. [66] Body mass index (BMI) is the most frequently used measure to define obesity, though mounting evidence suggests that accumulation of body fat around the waist (abdominal or central adiposity) may also predict risk independent of BMI. [70,71]

Abnormalities in renal structure and function have been noted in obese individuals. The most commonly described structural abnormalities are glomerulomegaly, mesangial expansion and sclerosis, and podocyte abnormalities, including a specific form of focal segmental glomerulosclerosis (FSGS) known as obesity-associated FSGS. [72,73] Functional abnormalities include glomerular hyperfiltration and proteinuria. [74] Diabetic kidney disease and obesity-related kidney disease share renal structural and functional abnormalities, and it is thus reasonable to hypothesize that their presence in the same individual may have additive effects. [75]

Several investigators have studied the association between obesity and diabetic kidney disease. A cross-sectional analysis from the the FinnDiane Study reported an independent association between abdominal obesity (waist circumference in men >102 cm and women >88 cm) and diabetic kidney disease in patients with type 1 diabetes. [76] In addition, De Boer *et al* [63] in a longitudinal study of 1279 individuals with type 1 diabetes, reported that the risk of incident microalbuminuria (defined as AER of ≥ 30 mg/24 h on two consecutive measurements) over 8 years of follow-up was 34% higher for each 10-cm greater waist circumference (hazard ratio 1.34, $p<0.05$). High correlation between waist circumference, waist to hip ratio and BMI was observed. Replacing waist circumference with BMI in the adjusted regression model resulted in similar hazard ratios. However, the authors did not find a significant association of waist circumference, BMI or waist to hip ratio with decline in creatinine clearance. Moreover, in a subgroup analysis of over 60,000 individuals with diabetes from an integrated health care delivery system in northern California, compared to participants with normal BMI ($18.5\text{--}24.9$ kg/m 2), the relative risk of ESRD was 1.9, 3.3 and

5.0 in participants who were overweight (BMI 25–29.9 kg/m²), had class I obesity (BMI 30.0–34.9 kg/m²), or class II obesity (BMI 35.0–39.9 kg/m²) respectively. [77]

Conversely, several investigators have failed to show a deleterious effect of obesity on diabetic kidney disease. Huang *et al.* in a prospective study of 105 patients with type 2 diabetes and CKD stage 3 or 4 followed for 24 months, concluded that a BMI 25kg/m² was protective against deterioration of renal function. [78] Furthermore, in a prospective observational cohort study of 1600 individuals with type 2 diabetes, BMI was not an independent predictor of eGFR decline among participants with baseline eGFR >60ml/min/1.73m². [79] Similarly, another prospective cohort study of patients with type 2 diabetes found no significant difference in the rate of CKD progression between obese and non-obese participants over a follow-up period of 30 months. [80]

If obesity is associated with diabetic kidney disease, it follows that its treatment, either with diet, medications or bariatric surgery should improve kidney disease. Several investigators have studied the effects of weight loss on diabetic kidney disease. Friedman *et al* [81] studied the effects of a 12-week low calorie weight loss diet in six obese individuals with type 2 diabetes and diabetic kidney disease (defined as eGFR <40ml/min/1.73m², and urine albumin excretion >30mg/day); the average weight reduction attained was 12% (median 118.5 kg at entry vs. 104.3 kg at the end of the study, p=0.03). The authors reported significant reductions in serum creatinine (from 3.54 to 3.13 mg/dL, p<0.05) and serum cystatin C (from 2.79 to 2.46 mg/L, p<0.05), and a 34% reduction in albuminuria which did not reach statistical significance. Another study evaluated the effect of a 4-week low calorie (11–19 kcal/kg/day) liquid protein diet on renal function and proteinuria in 22 obese participants with urinary albumin excretion >300 mg/day and serum creatinine <3.0 mg/dL. [82] Participants experienced significant weight loss (median BMI decreased from 30.4 to 28.2 kg/m², p<0.01), and visceral fat loss assessed by computed tomography (233 to 215 cm², p<0.05). Median proteinuria decreased from 3.27g/24hr to 1.50g/24hr, p<0.01. Serum creatinine also decreased (from 1.96 mg/dL to 1.49 mg/dL, p<0.01). However, these studies are limited by the small number of participants, and short intervention and follow-up periods. Heneghan *et al* [83] conducted a retrospective study of 52 participants with type 2 diabetes who had bariatric surgery for obesity and were followed for at least 5 years. Serial measurements of urine albumin-to-creatinine ratio (UACR) were performed. The authors found a significant correlation between postoperative UACR and weight loss. Fifty eight percent of participants with preoperatively albuminuria had experienced remission to normal UACR 5 years after surgery. Similarly, a retrospective study of 23 obese patients with type 2 diabetes and micro- or macroalbuminuria, laparoscopic adjustable gastric banding appeared to reduce albuminuria. [84] While these studies may suggest a role for weight loss to improve diabetic kidney disease, some limitations must be noted. It is not clear if participants had diabetic kidney disease, obesity- related structural renal abnormalities causing proteinuria or both, as most participants did not undergo renal biopsy. It is thus likely that improvements in renal function might be due to amelioration of the obesity-related lesions with weight loss, rather than improvement in diabetic kidney disease per se. Secondly, as expected given that obesity is associated with insulin resistance, most participants had improved glycemic indices and blood pressure control with weight loss,

which could have contributed to the observed improvement in kidney function. Additional research studies with larger samples are needed to improve our understanding of the association of obesity and weight loss with diabetic kidney disease progression.

Conclusions

Based on the available evidence from epidemiologic and clinical research studies, it is reasonable to recommend regular physical activity and abstinence from smoking for patients with diabetic kidney disease. Furthermore, personalized dietary counseling should be offered according to clinical and laboratory parameters, and a high protein diet should in general be avoided. In patients with morbid obesity weight loss appears to be a very promising treatment for diabetic nephropathy. However, additional studies are needed to better understand the association between obesity, weight loss and diabetic kidney disease.

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Figure 1.
Proposed mechanisms by which dietary protein could affect renal function.

Table 1

Lifestyle factors which could impact diabetic kidney disease

Diet
- High vs. low protein
Physical Activity
- Intensity
- Frequency/Duration
Cigarette smoking
Obesity
- Body mass index
- Waist circumference